(12) UK Patent Application (19) GB (11) 2 148 713 A

(43) Application published 5 Jun 1985

(21) Application No 8426765

(22) Date of filing 23 Oct 1984

(30) Priority data

(31) 545349 (32) 24 Oct 1983 (33) US
545350 24 Oct 1983

(51) INT CL[4]
A61K 31/20 A23D 3/00 5/00 C07C 51/487

(52) Domestic classification
A5B 26Y 401 406 40Y J
C2C 200 201 20Y 30Y 366 367 37X 43X 628 67Y 800 802 80Y CM VD
U1S 1089 2415 A5B C2C

(56) Documents cited
None

(58) Field of search
A5B

(71) Applicant
Century Laboratories Inc., (USA—New York), 99 Soundview Drive, Port Washington, New York 11050, United States of America

(72) Inventor
David Rubin

(74) Agent and/or address for service
Mathys & Squire, 10 Fleet Street, London, EC4Y 1AY

(54) Pharmaceutical composition and food product comprising higher fatty acids

(57) A pharmaceutical composition includes a combination of eicosapentaenoic acid and/or docosahexaenoic acid together with one or more of dihomo-γ-linolenic acid, cis-linoleic acid and γ-linolenic acid. This particular combination of fatty acids may also be administered in the form of a food product such as margarine or cooking oil. The composition causes lowering of blood chloesterol and triglyceride levels. The fatty acids used in this composition may be separated from mixtures thereof or from natural sources thereof by iodinating the double bonds in the starting fat or oil, saponifying, extracting the iodinated fatty acids, methylating and separating by column chromatography, and then deiodinating.

GB 2 148 713 A

SPECIFICATION

Combined Fatty Acid Composition for Lowering Blood Cholesterol and Triglyceride Levels

Field of the Invention

The present invention relates to pharmaceutical compositions and food products, and more particularly, to such compositions or food products containing a specific combination of fatty acids which can be used for the treatment of a human being or other mammal in order to lower the blood cholesterol and triglyceride levels of the subject.

Background of the Invention

It is known that Greenland Eskimos rarely suffer from atherosclerotic cardiovascular diseases. This fact has been attributed to the consumption of high amounts of fish oil. The active ingredients in fish oil are (all-Z)-5,8,11,14,17-eicosapentaenoic acid, sometimes designated 20:5ω3 fatty acid (hereinafter referred to as "EPA") and (all-Z)-4,7,10,13,16,19-docosahexaenoic acid, sometimes designated 26:6ω3 fatty acid (hereinafter referred to as "DHA"). EPA and DHA are known to be precursors in the biosynthesis of the prostaglandin PGE_3.

The above alternate designations, such as 20:5ω3, refer to the total number of carbon atoms in the chain, before the colon; the number of unsaturated bonds, after the colon; and the number of carbon atoms from the end opposite the carboxylic acid at which the first unsaturation appears, following the omega. Members of a given omega series of fatty acids, e.g. ω3, can usually be converted to acids of differing lengths and total number of unsaturations by normal bodily enzymes, but it is generally impossible to change a compound from one omega series to another, e.g. ω3 to ω6. This is because bodily enzymes generally cause changes of length and unsaturation to occur starting from the carboxylic acid end of the chain.

It is disclosed in British patents 1,604,554 and 2,033,745 that EPA can be used to treat effectively, or provide effective prophylaxis against, thromboembolic conditions such as myocardial infarctions, strokes, or deep vein thrombosis during surgical operations. They disclose the extraction of EPA from fish oil, such as cod liver oil or menhaden oil. The EPA may be administered by replacing butter or ordinary margarine by a special margarine formulated so that in normal usage the recipient would receive the required amount of the EPA.

This process has not achieved widespread attention, despite the fact that it uses a natural substance which can readily be incorporated into the daily diet. One reason may be due to the difficulty of efficiently separating EPA from natural fish oils to obtain a pure product at reasonable cost. Another reason may be that the effects of administration of EPA are not as dramatic as had been anticipated.

Summary of the Invention

It is an object of the present invention to eliminate the above-discussed deficiencies in the prior art.

It is another object of the present invention to provide improvements in compositions of the type of British patents 1,604,554 and 2,033,745.

It is a further object of the present invention to provide a composition which has superior therapeutic effects compared to those of the prior art.

It is yet another object of the present invention to provide a therapeutic composition containing naturally obtainable fatty acids which will serve to reduce blood cholesterol and triglyceride levels.

It is still another object of the present invention to provide a therapeutic composition which will increase the PGE_1:PGE_2 ratio in the patient and increase the absolute amount of PGE_1 in the system.

These and other objects are obtained through the simultaneous administration of one or more of EPA and DHA, together with one or more of dihomo-γ-linolenic acid (8,11,14-eicosatrienoic acid), i.e., 20:3ω6 fatty acid, (hereinafter referred to as "DHLA"), cis-linoleic acid ((Z,Z)-9,12-octadecadienoic acid), i.e., 18:2ω6 fatty acid, and γ-linolenic acid, ((Z,Z,Z-6,9,12-octadecatrienoic acid), i.e., 18:3ω6 fatty acid, either in the form of a pharmaceutical dosage or in the form of a food product such as margarine or cooking oil, or in the form of skin ointments or lotions for topical administration.

Detailed Description of Preferred Embodiments

The prostaglandins are a family of substances showing a wide diversity of biological effects. Prostaglandins of the 1-, 2- and 3-series, respectively, incorporate one, two or three double bonds in their basic 20-carbon carboxylic fatty acid structure which includes a 5-member cyclopentene ring.

The 1-series of prostaglandins are strong vasodilators and inhibit cholesterol and collagen biosynthesis, as well as platelet aggregation. On the other hand the 2-series prostaglandins are known to enhance platelet aggregation, cholesterol and collagen biosynthesis, and also to enhance endothelial cell proliferation. The main effect of the 3-series prostaglandins, particularly PGE_3, is the suppression of the 2-series prostaglandins.

The precursor of the 2-series prostaglandins is arachidonic acid ((all Z)-5,8,11,14-eicosatetraenoic acid), i.e., 20:4ω6 fatty acid. DHLA is the precursor for the 1-series prostaglandins, and, as indicated hereinabove, EPA and DHA are the precursors for the 3-series prostaglandins.

It is believed that the effectiveness of EPA and DHA in preventing atherosclerotic cardiovascular

diseases lies both in their effect as a precursor for prostaglandin PGE_3, which suppresses the 2-series prostaglandins, as well as the fact that the EPA and/or DHA itself competes with arachidonic acid on the same enzymatic system and thus inhibits the biosynthesis of 2-series prostaglandins. This inhibition of the 2-series prostaglandins results in an increase of the ratio of PGE_1:PGE_2.

In order to improve the effects of the administration of EPA and/or DHA alone, by further increasing the PGE_1:PGE_2 ratio, as well as effecting an increase in the absolute amount of PGE_1 in the system, DHLA should be administered simultaneously with the pure EPA and/or DHA. Since cis-linoleic acid and γ-linolenic acid both form DHLA metabolically within the body, either or both of these fatty acids may be substituted, in whole or in part, for DHLA.

It has been found that the combination of EPA (and/or DHA) and DHLA (and/or cis-linolenic acid and/or -linolenic acid) causes a substantial reduction in blood cholesterol and triglycerides. Recent research has definitely linked blood cholesterol levels with incidence of coronary heart disease (*JAMA*, 251, 351—364 (1984) and *JAMA* 251, 365—374 (1984)). Additionally, it is expected that such a combination will have other beneficial therapeutic properties. For example, it is known that in schizophrenia, rheumatoid arthritis and other collagen and auto-immune diseases, as well as in some forms of cancer, there are evidences of extremely low levels of PGE_1 and high levels of PGE_2. Thus, it is expected that the combination of the present invention may be able to serve as an effective treatment for such conditions. Furthermore, the anti-inflammatory effect of cortico-steroids and the pain killing effect of aspirin are believed to be due to their suppressing effect of PGE_2 formation. Thus, the use of the combination of the present invention can be expected to be a natural and most effective anti-inflammatory pain killing agent.

The dose of the composition of the present invention, comprising a combination of EPA (and/or DHA) and DHLA (and/or cis-linoleic acid and/or γ-linolenic acid), needed for therapeutic or prophylactic effect will vary with the route of administration and the nature of the condition being treated, but will generally be at least 1 gram, preferably from 1.5 to 3 grams, per day. This is the dose for an average 70 kg man, and the dose for other men or animals will vary pro rata according to their weight, i.e. about 20—40 mg/kg.

The relative amounts of EPA (and/or DHA) and DHLA (and/or cis-linoleic acid and/or γ-linolenic acid) in the composition of the present invention is preferably 1:1, although the ratio may vary from 3:1 to 1:3.

The EPA (and/or DHA) and DHLA (and/or cis-linoleic acid and/or γ-linolenic acid) need not be administered as the acids themselves but may be used as their pharmaceutically acceptable salts, esters or amides. Esters or amides which can be converted *in vivo* to the acid and other pharmaceutically acceptable products may be used, the preferred ester being the ethyl ester. The preferred salts are the sodium or potassium salts, or any other pharmaceutically acceptable solid salt, as these are suitable for making into tablets.

While it is preferred to administer the composition of the present invention orally, as this is a convenient route for routine administration, the active compounds may be administered by any route by which it may be successfully absorbed, e.g., parenterally (i.e. subcutaneously, intramuscularly or intravenously), rectally or vaginaly, or topically, for example as a skin ointment or lotion.

While it is possible for the active compounds to be administered as such, as a simple mixture of components, it is preferable to present them as a pharmaceutical formulation. The formulations, both for veterinary and for human medical use, of the present invention comprise the active compounds as defined, together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic ingredients, although other unsaturated fatty acids should be avoided, particularly arachidonic acid. The carrier(s) must be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof. Formulations include those suitable for oral, rectal, vaginal, intrapulmonary or parenteral (including subcutaneous, intramuscular and intravenous) administration. Formulations for oral administration, such as tablets or capsules are preferred.

The EPA (and/or DHA) — DHLA (and or cis-linoleic acid and/or γ-linolenic acid) combination may also be administered by replacing better and/or ordinary margarine by a special margarine, e.g. of the emulsion type, formulated so that in normal usage the recipient would receive the required amount of the combination. Cooking oils and fats may also be similarly formulated to contain the composition of the present invention.

The EPA (and/or DHA) and DHLA (and/or cis-linoleic acid and/or γ-linolenic acid) used in the compositions of the present invention should be as pure as possible. EPA and/or DHA cannot be used in the form of fish oil directly, as the use of the amount of fish oil necessary in order to provide the desired amount of EPA and/or DHA would provide excessive calories and potentially toxic amounts of vitamins A and D. Thus, pure EPA and/or DHA should be extracted from the fish oil. The presence of unsaturated fatty acids other than EPA, DHA, DHLA, cis-linoleic acid and γ-linolenic acid should be avoided.

Substantially pure EPA and/or DHA may be extracted from fish oil, such as cod liver oil, by means of the process set forth, for example, in U.S. Patent 4,377,526. Alternatively, the separation may be accomplished by a novel process of the present applicant involving iodination of the double bonds of the unsaturated fatty acids in the starting fat or oil. Such iodination permits protection of the fatty acids from oxidation during further processing, and increases the resolution of the fatty acids upon eventual column and chromatography. After iodination, the fat or oil is saponified and the iodinated fatty acid extracted from the saponification mixture. The iodinated fatty acids are then methylated and separated by column chromatography, after which the desired fractions are deiodinated. This process can be used not only for

the separation of EPA and DHA from fish oils, but also for the separation and extraction of other unsaturated fatty acids, such as α-linolenic acid and γ-linolenic acid from the triglyceride forms in which they naturally occur in, for example, soybean oil, cottonseed oil, safflower oil, oil of evening primrose, etc. The separation of any unsaturated fatty acid can be facilitated by means of the present iodination process.

The starting material in the present process can be a natural fat or fatty oil in which the first step is iodination followed by saponification. However, the starting material may also be any mixture of unsaturated fatty acids which are difficult to separate, in which the first step will be iodination but no saponification will be required as the starting material is not a triglyceride.

Iodination takes place by adding iodine, in an organic solvent, preferably 20% ethanolic solution, slowly to the starting material until the color fails to disappear in the starting material. This reaction takes place at room temperature under continuous stirring.

The saponification step can take place in any conventional manner such as, for example, with a 20% ethanolic solution of KOH for two hours.

The iodinated fatty acid is extracted from the saponification mixture by means of any conventional procedure, for example, extraction with ether.

The next step is the methylation of the iodinated fatty acids to prepare them for column chromatography. Again, this is a conventional step and may be done, for example, with 5% hydrogen chloride in methanol.

Finally, the fatty acids are separated by means of column chromatography. The column chromatography is carried out in a known manner with a conventional elution mixture. While resolution among the various fatty acids is very poor in the conventional processes, the resolution is greatly improved when the fatty acids are iodinated at the time of column chromatography. The column may be packed with silica gel as is conventional and the elution solution may be any conventional solution, such as hexane-ether-acetic acid (85-10-5).

After the fractions are obtained from the column, the fatty acids are deiodinated using, for example, silver nitrate.

While specific reagents and process conditions are set forth for the various steps of the present process, it should be understood that those skilled in the art will readily be aware of other reagents and conditions in order to carry out the steps once the desirability of each step is known. The critical factor is the concept of iodination prior to chromatography in order to increase the resolution and to protect the fatty acids from oxidation.

Furthermore, although the separation is accomplished by column chromatography in the above description, it should be understood that other means of separation may be used as, for example, high speed centrifugation. The resolution will also be improved by iodination in such other separation means.

The following is an example of a method for the separation of EPA and DHA from cod liver oil in accordance with this process.

Preparative Example

A 20% ethanolic solution of iodine is added slowly to 300 g of cod liver oil. The iodine is added as long as its color disappears in the oil. The reaction takes place at room temperature under continuous stirring. When iodination is completed, the iodinated oily solution is saponified with 20% ethanolic solution of KOH for two hours. The iodinated fatty acid, 260 g, is extracted with ease from the saponification mixture.

The iodinated fatty acids are then methylated with 5% hydrogen chloride in methanol. The EPA and the DHA are separated by column chromatography (silica-gel 1,500 g, Kieselgel 70—230 mesh, Merck). The elution is done with 5 liters hexane-ether-acetic acid (85-10-5). The first fraction to be extracted is the iodinated DHA. The second fraction is iodinated EPA.

Once the substantially pure methylated and iodinated fatty acid mixture is obtained, it may also be separated by other conventional techniques, such as high speed centrifugation or distillation. Deiodination takes place by shaking the iodinated Me-DHA and Me-EPA, separately, with 10% aqueous solutions of silver nitrate. Precipitates of silver-iodine appears and the organic phases are separated. The same procedure is repeated until no more precipitation occurs. Microanalysis, HPLC and NMR proved that the desired products are obtained. The yield is above 90%, the purity 96—100%. There is no need to carry out the procedure under nitrogen since the fatty acids are saturated with iodine, thus preventing oxidation from taking place.

The following clinical tests illustrate the synergistic effects which are obtained when using the combination of the present invention as compared to the effects of each of the components administered alone.

Therapeutic Example

Thirty-six outpatients, ages 35—75, males and females, were divided into three groups of twelve. Each group added to their normal diet 5 cc/day of free fatty acids for 45 days. Group I added 5 cc/day of substantially pure EPA. Group II added to their diet 5 cc/day of substantially pure cis-linoleic acid, and group III added to their diet 3 cc/day of substantially pure EPA and 2 cc/day of substantially pure cis-linoleic acid. By the term "substantially pure" is meant a purity of about 96—100%.

Blood cholesterol and triglycerides were tested one day before the treatment began and after 45 days of treatment. The results of these treatments are set forth in Tables I, II and III hereinbelow:

TABLE I
5 cc/day Pure EPA

Patient No.	Age	Sex	Total Cholesterol 1 Day Before Treatment mg %	Total Cholesterol After 45 Days mg %	Triglycerides 1 Day Before Treatment mg %	Triglycerides After 45 Days mg %
1	45	M	250	220	130	102
2	45	M	248	220	115	95
3	47	M	230	210	102	90
4	73	M	270	240	95	90
5	60	F	280	240	115	95
6	56	M	265	260	120	105
7	54	F	215	205	95	90
8	52	F	285	250	115	100
9	63	M	300	250	110	95
10	64	M	350	260	160	105
11	55	M	190	190	95	80
12	35	M	200	190	90	90±7
Average:			256.9±43.2	227.9±24.4	111.8±18.6	94.95±
% reduction:				11.2%		15%

TABLE II
5 cc/day Pure cis-Linoleic Acid

Patient No.	Age	Sex	Total Cholesterol 1 Day Before Treatment mg %	Total Cholesterol After 45 Days mg %	Triglycerides 1 Day Before Treatment mg %	Triglycerides After 45 Days mg %
1	47	M	190	200	95	95
2	75	F	350	340	90	95
3	60	F	200	205	110	105
4	60	F	220	220	115	100
5	55	F	240	210	90	100
6	37	M	270	260	105	95
7	40	M	220	230	80	80
8	45	M	400	350	165	150
9	62	F	310	300	140	140
10	54	M	230	220	115	115
11	52	M	260	250	110	110
12	61	F	215	215	130	125
Average:			265.3±61.75	250±50	112±22.8	109.16±19.4
% reduction:				5%		2%

TABLE III
3 cc/day Pure EPA and 2 cc/day Pure cis-Linoleic Acid

Patient No.	Age	Sex	Total Cholesterol 1 Day Before Treatment mg %	Total Cholesterol After 45 Days mg %	Triglycerides 1 Day Before Treatment mg %	Triglycerides After 45 Days mg %
1	48	M	450	260	160	90
2	60	M	310	240	70	40
3	45	M	257	210	106	50
4	40	M	305	250	98	45
5	54	M	210	200	95	55
6	35	F	210	190	95	45
7	40	M	290	240	100	70
8	61	F	270	220	116	45
9	45	F	240	215	95	80
10	50	F	210	190	75	60
11	64	M	300	220	130	80
12	64	M	190	180	55	50
Average:			270.1±67.5	217.9±24.4	99.5	59.16±16
% reduction:				19.3%		40.5%

While the administration of 5 cc/day of EPA alone provided a reduction in serum cholesterol and triglyceride levels during the 45 days of treatment, i.e. an average reduction of 11.2% for total cholesterol and 15% for triglycerides, the effect of the administration of pure cis-linoleic acid alone for 45 days is almost insignificant. In fact, in many patients the cholesterol level actually rose.

A definite synergism, however, is observed by administration of the combination of 3 cc EPA plus 2 cc cis-linoleic acid per day. By use of the combination, a very significant reduction of serum cholesterol (an average of 19.3% decrease) and serum triglycerides (an average of 40.5% decrease) is observed.

It will be obvious to those skilled in the art that various changes may be made without departing from the scope of the invention and the invention is not to be considered limited to what is described in the specification.

CLAIMS

1. A pharmaceutical composition for causing a reduction of blood cholesterol and triglyceride levels, consisting essentially of an effective amount of a combination of a first component selected from the group consisting of 5,8,11,14,17-eicosapentaenoic acid, 4,7,10,13,16,19-docosahexaenoic acid and a combination thereof, and a second component selected from the group consisting of dihomo-γ-linolenic acid, cis-linoleic acid, γ-linolenic acid and combinations thereof, said first and second components being present in relative amounts of 3:1 to 1:3.

2. A composition in accordance with claim 1, further including a pharmaceutically acceptable excipient.

3. A composition in accordance with claim 1, wherein said composition is substantially free of other unsaturated fatty acids.

4. A composition in accordance with claim 1, wherein said first component is 5,8,11,14,17-eicosapentaenoic acid.

5. A composition in accordance with claim 1, wherein said second component is cis-linoleic acid.

6. A composition in accordance with claim 4, wherein said second component is cis-linoleic acid.

7. A food product containing a substantial amount of at least one fatty acid, characterized in that said at least one fatty acid present in said food product consists essentially of a combination of a first component

selected from the group consisting of 5,8,11,14,17-eicosapentaenoic acid, 4,7,10,13,16,19-docosahexaenoic acid and a combination thereof, and a second component selected from the group consisting of dihomo-γ-linolenic acid, cis-linoleic acid, γ-linolenic acid and combinations thereof, said first and second components being present in relative amounts of 3:1 to 1:3.

8. A food product in accordance with claim 7 which is substantially free of other unsaturated fatty acids.

9. A food product in accordance with claim 7, wherein said first component is 5,8,11,14,17-eicosapentaenoic acid.

10. A food product in accordance with claim 7, wherein said second component is cis-linoleic acid.

11. A food product in accordance with claim 9, wherein said second component is cis-linoleic acid.

12. A composition in accordance with claim 1, wherein the unsaturated fatty acids used therein are extracted from natural sources thereof by the steps of:
iodinating the double bonds of the unsaturated fatty acids and triglycerides in the source material;
saponifying the obtained mixture;
extracting the iodinated fatty acids from the saponification mixture;
methylating the iodinated fatty acids;
separating the fatty acids by column chromatography; and
deiodinating the desired fraction.

13. A food product in accordance with claim 7, wherein the unsaturated fatty acids used therein are extracted from natural sources thereof by the steps of:
iodinating the double bonds of the unsaturated fatty acids and triglycerides in the source material;
saponifying the obtained mixture;
extracting the iodinated fatty acids from the saponification mixture;
methylating the iodinated fatty acids;
separating the fatty acids by column chromatography; and
deiodinating the desired fraction.

14. A method for extracting pure fatty acids from natural sources thereof, comprising:
iodinating the double bonds of the unsaturated fatty acids and triglycerides in the source material;
saponifying the obtained mixture;
extracting the iodinated fatty acids from the saponification mixture;
methylating the iodinated fatty acids;
separating the fatty acids by column chromatography; and
deiodinating the desired fraction.

15. A composition in accordance with claim 1, wherein the unsaturated fatty acids used therein are separated from mixtures of fatty acids by the steps of:
iodinating the double bonds of the unsaturated fatty acids in the mixture;
methylating the iodinated fatty acids;
separating the fatty acids by column chromatography; and
deiodinating the desired fractions.

16. A food product in accordance with claim 7, wherein the unsaturated fatty acids used therein are separated from mixtures of fatty acids by the steps of:
iodinating the double bonds of the unsaturated fatty acids in the mixture;
methylating the iodinated fatty acids;
separating the fatty acids by column chromatography; and
deiodinating the desired fractions.

17. A method for separating fatty acids from mixtures thereof, comprising:
iodinating the double bonds of the unsaturated fatty acids in the mixture;
methylating the iodinated fatty acids;
separating the fatty acids by column chromatography; and
deiodinating the desired fractions.

Printed in the United Kingdom for Her Majesty's Stationery Office, Demand No. 8818935, 6/1985. Contractor's Code No. 6378.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

The application was originally made under the Patent Cooperation Treaty with the Japanese Patent Office acting as the receiving office on (86) 27 June 1981, being given an application number PCT/JP81/00148. The application was searched by the Japanese Patent Office acting as the International Search Authority (ISA), and published by the International Bureau on (87) 21 Jan 1982 under serial number WO82/00095 in the Japanese language. The text of the application is contained in the publication made by the International Bureau as above identified. The accompanying text being being an English translation thereof

(12) UK Patent Application (19) GB (11) 2 090 529 A

(21) Application No 8204905
(22) Date of filing
27 Jun 1981
(30) Priority data
(31) 55/088072
(32) 27 Jun 1980
(33) Japan (JP)
(43) Date of issue
14 Jul 1982
(51) INT CL³ (AS GIVEN BY ISA) A61K 31/20 31/16 31/23
(52) Domestic classification
A5B 382 38Y 401 406 40Y 410 41Y H
(56) Documents cited by ISA
JP A 55–15444
JP A 54–154533
(58) Field of search by ISA
INT Cl A61K 31/20 A61K 31/23 A61K 31/16 C07C 57/03 C07C 69/587 C07C 103/133

(71) Applicant
Nippon Oil and Fats Co Ltd
10–1 Yuraku-Cho
1-Chome
Chiyoda-Ku
Tokyo 100
Japan
(72) Inventors
Chikayuki Naito
Jun Kawai
Yoshiaki Miyazaki
(74) Agents
Eric Potter & Clarkson
5 Market Way
Broad Street
Reading RG1 2BN
Berkshire

(54) Thrombosis-prophylatic and curing agent

(57) A thrombosis-preventing and curing agent containing at least one member selected from among (all-Z)-4,7,10,13,16,19-docosahexanoic acid, pharmaceutically acceptable salt, ester and amide thereof as effective ingredient. This agent is absorbed through the intestine so well that it can be used internally, is stable in blood and shows excellent effect of preventing blood platelets from agglutinizing.

GB 2 090 529 A